Insulin Paving Way to Breast Cancer and Its Current Clinical Therapies

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Abstract **- The world booms with insulin and its alarming diseases. Insulin is secreted from islets of Langerhans and regulates various metabolic processes, facilitates glucose uptake, and promotes cell division. Several protooncogenes are mutated to an oncogene by various signaling pathways in which insulin paves a major role in increasing the risk for initiation of developing varied solid tumors, especially in larger women's diabetic populations. Insulin involves mainly in two signaling pathways include PI3K and MAPK pathways. Activation of these pathways leads to glucose and lipid homeostasis, inhibition of the proapoptotic pathway, translocation of GLUT-4 receptor to membrane and fat to increase glucose uptake, and inhibition of glycolysis and gluconeogenesis. Among Luminal A & B and TNBC types PI3K and MAPK pathway mainly involves in the proliferation of survival translation, these are regulated by tumor suppressor genes such as p53, PTEN, BRCA1 & BRCA2.**

Index terms: **Insulin, Breast cancer, PI3K, and MAPK.**

I. INTRODUCTION

Insulin is a peptide hormone that is secreted by the pancreatic islets of Langerhans cells. It regulates carbohydrate, lipid, and protein metabolism, facilitates cellular glucose uptake, and promotes cell division and proliferation through its mitogenic effects (1). Since insulin exerts a central role in the control of metabolic homeostasis and deregulation of its activity is associated with disease states such as diabetes, obesity, and metabolic syndrome (2). The eighth most common cause of mortality worldwide is diabetes, whereas the second most common cause is cancer (3). The linkage between these two diseases is insulin (4). The long-term administration or increased levels of insulin increase the risk for diabetic patients by 20-80 % to cause cancer more than non-diabetic patients (4)(5). In 2019 about 1.55 million people died of diabetics and 10.08 million people died of cancer among that 8-18 % of patients are having diabetics (3). The worldwide pervasiveness of diabetics was estimated to rise from 171 million in 2000 to 366 million in 2030 and About 26.9% of all people over 65 have diabetes and 60% have cancer. Age, sex, ethnicity, alcohol, cigarettes, food, physical activity, obesity, and BMI appear to further complicate the relationship as risk factors for both illnesses (4). The risk ratio for all site cancer linked to diabetes was 1.27 percent in women and 1.19 percent in men, according to a meta-analysis of 121 cohorts involving 20 million people and roughly 1 million cancer incidents. Comparing men and women with diabetes, the risk was 6 percent higher for women than men (6). A July 2018 study confirmed that both type 1 and type 2 diabetes put people at greater risk of developing certain cancers(7). Bigger research done in China found that diabetics are more likely to acquire 11 cancers in males and 13 cancers in women. Men had a significantly higher risk — almost double — for prostate cancer. But type 2 diabetes was also linked with higher risks of leukemia, skin cancer, thyroid cancer, lymphoma, kidney cancer, liver cancer, pancreatic cancer, lung cancer, colorectal cancer, and stomach cancer. Men with diabetes had a lower risk for esophageal cancer. Women with type 2 diabetes had a twofold higher risk of nasopharynx cancer. They also had elevated risks for liver cancer, esophageal cancer, thyroid cancer, lung cancer, pancreatic cancer, lymphoma, uterine cancer, colorectal cancer, leukemia, breast cancer, cervical cancer, and stomach cancer (8). In the same way Insulin potentiation therapy (IPT) is an alternative cancer therapy that uses insulin to potentiate the effects of chemotherapy and other medications. In this review, we elaborately discuss the insulin signaling pathway and the link between the insulin and pathway for the development of breast cancer in females.

II. INSULIN SIGNALING PATHWAYS

Insulin attaches to insulin receptors (IRs) on target cell membranes after being released by pancreatic cells and traveling throughout the body. Insulin receptor substrate (IRS) is phosphorylated as a result, and two main signaling pathways—the PI3K/Akt pathway and the mitogen-activated protein kinase (MAPK) route—are subsequently activated (9).

A. Phosphoinositide-3-kinase–protein kinase B/Akt (PI3K-PKB/Akt)

Insulin (INS) binds in insulin receptor tyrosine kinase (INSR) which activates the insulin receptor substrate(IRS) by tyrosine phosphorylation, this IRS phosphorylates the PI4,5bisphosphate to PI 3,4,5 triphosphate(PI3K).this activates the 3-phosphoinosital dependent protein kinase (PDK1) which activates the protein kinase B(Akt).on activation of Akt leads to various function in the body to maintain homeostasis through regulation of multiple cellular function. They are, it inactivates the Rapamycin complex 1(mTORC1) which gives a way for promotion of protein synthesis. Also inhibits the pro-apoptotic pathway by phosphorylation of BCL2 death promotor gene (BAD) which increase the cell survival.

PDK1 phosphorylates the atypical protein kinase (aPKC) which leads to inhibition of sterol regulatory binding proteins (SREBP1c) and gets translocated to the cell nucleus and transcribe gene for fatty acid and cholesterol synthesis by inhibition of gene such as ACC, FAS, PYK gene to maintain lipid homeostasis.

On activation of Akt it regulates the translocation of insulin sensitive glucose transporter (GLUT 4) to membrane and fat to increase the glucose uptake to maintain the glucose homeostasis and also insulin receptor (IR) facilitates the phosphorylation of Cbl associated protein(CAP) to form CAP complex.

Also Akt phosphorylate the glycogen synthase kinase 3β(GSK-3β) and this phosphorylates the glycogen synthase (GYS) leads to formation of glycogen at the same time this process also activated through inhibition of protein phosphatase 1(PP1) which dephosphorylates the phosphorylase kinase (PHK) and the phosphorylate glycogen phosphorylase to form glycogen,both these way to generate glycogen are to maintain the glucose homeostasis.

Also Akt phosphorylates the phosphodiesterase 3(PDE3) which activates cAMP and protein kinase A (PKA) this phosphorylates the hormone-sensitive lipase (HSL), which inhibits the antilipolytic to maintain the lipid homeostasis. Also, Akt phosphorylates the Forkhead box 01(FOXO1) leading to the synthesis of the DNA for G6PC, FBP, and PEPCK protein, these are involved in the inhibition of glycolysis and gluconeogenesis (9)(10).

B. Mitogen-activated protein kinase / Ras-Raf-MEK-ERK pathway)

Activation of INS1 by insulin on binding with the INSR which binds to growth factor receptor bound protein 2 (Grb2) activates the SOS then activates the Ras and activating the C-Raf activates the MAPK/Erk kinase (MEK).this phosphorylates the extracellular signal-regulated kinase (Erk) this get translocated to the nucleus in the cell. there phosphorylation and transcription are activated by a factor such as ELK1. This process completely results in the promotion of cell division, protein synthesis, and cell growth (9) (10).

III. PATHWAY FOR BREAST CANCER

From the past few decades many clinical and non-clinical trials have been conducted for determination of pathway for developing cancer. There are different type of breast cancer developed such as triple negative breast cancer, luminal A, luminal B breast cancer based o their way of developing of cancer.

In this pathway there are some oncogenes such as FGFR1, PI3KCA, CCND1 on overexpression of these gene leads to development of BC. To suppress these genes there are some tumors suppressing genes that are involved in preventing the proliferation of cancer cells by interrupting the cell cycle in the two check points by preventing the completion of the cell cycle. They are p53, PTEN (phosphatase and tension homolog), Brca1 & Brca2 (Breast cancer gene1&2).

In breast cancer, cell proliferation is processed through various signaling pathways such as ERK signaling (MAPK pathway), PI3K signaling, WNT signaling, Notch signaling, cell cycle, and transcription which all are having a major function in proliferation survival translation and cell proliferation. The p53 signaling pathway is involved in the inhibition of cancer cells.

Insulin Mainly acting on PI3K and MAPK pathway are involved in the proliferation survival translation in the breast cancer cell. In PI3k signaling the

overexpression and mutation of these genes leads to development of cancer, they are

1) EGFR-overexpression
2) EGBB2- overexpression
3) Amplified FGFR
4) Mutation activated PI3K
5) Amplified PI3K
6) Mutation-inactivated PTEN.

Proteins such as FGF (fibroblast growth factor), EGF (epidermal growth factor), and IGF (insulin growth factor) are the proteins that are mainly involved in activating these 2 signaling pathways.

Overexpression of these proteins tends to activate this pathway by binding FGF to FGFR1 (fibroblast growth factor receptor 1), EGF to EGFR (epidermal growth factor receptor), and IGF to IGF1R (insulin growth factor 1 receptor). And also, HER2(human epidermal growth factor 2) promotes the growth of cancer cells. These are the receptor that is present in the cell membrane. This activation of receptors tends to develop the 3 types of cancer such as TNBC, Luminal A & B.

In PI3K pathway activation leads to activation of PIP3 which activates the Akt to mTOR, leads to activation of S6K gene to proliferation of survival translation. In this pathway PTEN dephosphorylates the PIP3 to prevent the activation of Akt which leads to prevent the proliferation of the cell.

In MAPK pathway activation of Grb2 activates the SOS then Ras and Raf then phosphorylates the MEK which then phosphorylates the ERK leads to proliferation of survival translation (10).

IV. LINK BETWEEN INSULIN AND BREAST CANCER:

Insulin binds to IGF-1R α subunit leads to the autophosphorylation of β subunit residues, which then act as a docking site to INS which activates these two PI3K and MAPK signaling pathways (11).

Here insulin exerts direct anabolic actions in neuron-like cells by activation of its cognate receptor(12).

Also, varied evidence from the clinical and pre-clinical trials shows that BC cells are having significantly higher IGF-1R when compared to normal breast cells. This becomes the therapeutic target for the treatment of BC by targeted drug therapy. Also, these studies show that the loss of tumor suppressor gene such as Brca1 & 2, p53, PTEN leads to an increase in IGF-1R expression in tumor cells which leads to increase the activation of these 2 signaling pathway leads to proliferation of survival translation and gene expression for protein synthesis (13).

V. DRUGS THAT ARE ACTING ON THIS PATHWAY FOR TREATMENT OF BREAST CANCER

There are various drugs that are involved in preventing and treating the breast cancer. In this part the drugs that are mainly acting on inhibition of the PI3K and MAPK pathway are discussed.

In PI3K pathway there are various inhibitors i.e. PI3K inhibitors (PI3Ki) including Alpelisib, Idelalisib and Copanlisib, have been approved by the Food and Drug Administration (FDA)(14) According to the targeted isoforms of class IA PI3Ks, PI3Ki can be classified into pan-PI3Ki, such as buparlisib and pictilisib isoform-specific PI3Ki, such as taselisib and alpelisib, and dual mTOR/pan PI3Ki, such as Dactolisib.

Alpelisib is the first oral PI3Ki that targets the p110α isoform selectively (IC_{50} = 4.6 nM) and it was the first approved PI3K inhibitor combined with Fulvestrant for patients with HR+/HER2− metastatic breast cancer (mBC) (15).

Taselisib is another oral class I isoform-specific PI3K inhibitor, as it exhibits equal inhibition of p110α, p110γ and p110δ (16). Buparlisib, an oral pan-PI3K inhibitor, targets all four isoforms of class I PI3K (17). Based on previous results of clinical trials, compared to pan-PI3K inhibitors, these isoform-specific PI3K inhibitors show improved tolerability and increased anticancer efficacy (18,19), Thus, more selective PI3K inhibitors are expected in the future.

Also, AKT inhibitors (Akti) are also available for the treatment of cancer, they are

1) PH domain inhibitors
2) Allosteric inhibitors and
3) ATP competitive inhibitors

PH domain and allosteric inhibitors are having poor pharmacokinetic and heavily toxic effects because of this ATP competitive inhibitors are mainly targeted for developing drugs. such as Ipatasertib and Capivasertib.

As a downstream molecule of the PI3K/AKT pathway, mTOR inhibitors can inhibit breast cancer cell growth. Everolimus was the first approved mTOR inhibitor for HR+/HER2− breast cancer and showed an improved

PFS in several clinical trials (19)(20). In MAPK pathway different classes MAPK inhibitor (MAPKi) drugs are used to prevent the proliferation of the breast cancer cell. They are

1) Selective BRAF V600E inhibitor (ATP competitive) – Vemurafenib, Dabrafenib, Encorafenib
2) Selective MEK1/2 inhibitor (ATP non-competitive) – Trametinib, Binimetinib
3) Selective MEK1 inhibitor (ATP non-competitive) - Cobimetinib
4) Selective EGFR inhibitor (ATP competitive) – Gefitinib
5) EGFR and HER2 inhibitor (ATP competitive) – Lapatinib(21)

VI.FUTURE PERSPECTIVES

From the above perspective we need to go for the insulin potentiation therapy. The goal of insulin potentiation therapy is to reduce the amount of chemotherapy required by allowing more of the medicine to enter cells. Insulin is given together with chemotherapy medications. This hypothesis has not, however, been validated. We the pharmacists should acknowledge this and must urge to develop targeted drug therapy for the future world.

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